REMARKS

Any fees that may be due in connection with the filing of this and the attached papers may be charged to Deposit Account No. 06-1050. If a Petition for Extension of Time is required, this paper is to be considered such Petition.

A Supplemental Information Disclosure Statement is enclosed.

Claims 1-21, 23-38, 40-83, 87-89, 93 and 99-121 are pending herein. Claims 65-68 have been withdrawn from consideration as allegedly being drawn to a non-elected species. Claims 22 and 39 are cacelled herein without prejudice or disclaimer. Applicant reserves the right to file continuation or divisional applications to any canceled subject matter.

Claims 1 and 117 are amended herein to incorporate the limitations of original claim 22. Claims 1 and 117 are also amended herein to replace the recitation of "subject" with "human." Basis for this amendment may be found, for example, in the specification as originally filed at page 29, lines 1-3. Claims 1, 63-65, 77, 78 and 117 are further amended herein to replace the term "derivative" with "pharmaceutically acceptable salt or hydrate." Basis for these amendments may be found, for example, in the specification as originally filed at page 10, lines 20-21.

INTERVIEW SUMMARY

The Examiner is thanked for the very helpful telephonic interview of August 9, 2004. Several of the rejections in the instant Office Action were discussed. Applicant respectfully submits that the amendments to the claims herein, the following Remarks, and the enclosed DECLARATION of BANERJEE place this application in condition for allowance. Applicant respectfuly requests that the Examiner contact Applicant's representative should any outstanding issues remain.

The rejection of the claims as allegedly being indefinite for recitation of "derivative" was discussed. Applicant agreed to consider replacing the recitation of "derivative" with "pharmaceutically acceptable salt or hydrate." Applicant has made such amendment to the claims herein.

The art of record was discussed. In particular, Hochrainer *et al.* (U.S. Patent No. 6,150,418) was discussed. Applicant's representative noted that Hochrainer *et al.* teaches highly concentrated formoterol compositions suitable for storage and that the instant claims are directed to formoterol compositions formulated at a lower concentration (*i.e.*, suitable for direct administration via nebulization). The Examiner expressed concern that the claims as currently written did not sufficiently distinguish the concentration recited therein from the concentrations taught in Hochrainer *et al.* Applicant's representative agreed to consider incorporating the limitations of claim 22 into claim 1 to further distiguish the instant claims from the cited art. Such amendment has been made herein.

The lack of stability of formoterol in aqueous solution was also discussed. Applicant's representative noted that formoterol is unstable in aqueous solution, and the the instant claims are directed to aqueous compositions of formoterol formulated to be stable during long term storage. The Examiner requested that evidence of the instability of formoterol in aqueous solution be provided. Porovided herein is an executed DECLARATION of BANERJEE provided data demonstrating the instability of formoterol in purified water. Thus, this DECLARATION demonstrates the role of water in the decomposition of formoterol.

REJECTION OF CLAIMS 1-64, 69-83, 87-89, 93 AND 99-121 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-64, 69-83, 87-89, 93 and 99-121 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Office Action alleges that the recitations of "subject," "derivative," "Britton-Robinson" and "Prideaux-Ward" are indefinite. Applicant respectfully submits that these terms no longer are present in the claims. Reconsideration and removal of this rejection is respectfully requested.

REJECTION OF CLAIMS 87-89 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 87-89 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement for "prevention" of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction. Applicant respectfully submits that this term no longer is present in the claims. Reconsideration and removal of this rejection is respectfully requested.

REJECTION OF CLAIMS 1-64, 69-83, 87-89, 99-112 AND 117-119 UNDER 35 U.S.C. §103

Claims 1-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Carling *et al.* (U.S. Patent No. 5,674,860) in view of Hochrainer *et al.* (U.S. Patent No. 6,150,418). It is alleged that Carling *et al.* teach a pharmaceutical compsition containing formoterol in combination with budesonide. It is further alleged that Hochrainer *et al.* teaches a pharmaceutical composition containing formoterol suitable for storage in water and ethanol. It is alleged that combination of these references results in the compositions of the instant claims. Applicant respectfully requests reconsideration of this rejection in view of the amendments herein and the following remarks.

Relevant Law

[I]n order to establish a prima facie case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The Instant claims

Instant claim 1 is directed to a pharmaceutical composition, comprising (i) formoterol, or a pharmaceutically acceptable salt or hydrate thereof; and (ii) a steroidal anti-inflammatory agent, or a pharmaceutically acceptable salt or hydrate thereof;

in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, the formoterol free base concentration is about 5 μg/mL to about 2 mg/mL, and the composition is formulated at a concentration for direct administration to a human in need thereof.

The teachings of the cited references and differences from the instant claims

Carling *et al.* teaches combination therapy using formoterol and budesonide in the treatment of asthma. Carling *et al.* teaches in Examples 1-3 DPI and MDI formulations of the above-referenced combination. While the cited reference does teach or suggest nebulizable formulations containing formoterol and budesonide, it does not teach or suggest nebulizable formulations of formoterol and budesonide that have a formoterol concentration of between about 5 μg/mL and about 2 mg/mL, and are stable during long term storage, as required by the instant claims.

Hochrainer *et al.* does not cure this defect in Carling *et al.* because, while Hochrainer *et al.* teaches highly concentrated compositions of formoterol suitable for storage, it does not teach or suggest compositions having a formoterol concentration of between about 5 μg/mL and about 2 mg/mL that are stable during long term storage. In contrast, Hochrainer *et al.* teaches, at column 2, lines 4-11, that the concentration of formoterol in the compositions taught therein is much higher – at least 10 mg/mL, preferably at least 75, 100 or 250 mg/mL:

> According to the invention the formoterol concentration in the active substance concentrate is between 10 mg/ml and 500 mg/ml. Preferably, the minimum concentration is at least 75 mg/ml. Preferred concentrations are between 100 mg/ml and 400 mg/ml, particularly between 250 mg/ml and 350 mg/ml.

Hochrainer *et al.* does not teach or suggest formoterol compositions at lower concentrations, as required by the instant claims, that are stable during long term storage, as required by the instant claims. Therefore, Hochrainer *et al.* does not cure the defects in Carling

et al., and the instant claims are not *prima facie* obvious over the teachings of Carling *et al.* in view of Hochrainer *et al.* Reconsideration and removal of this ground of rejection is respectfully requested.

REJECTION OF CLAIMS 1-64, 69-83, 87-89, 99-112 AND 117-119 UNDER 35 U.S.C. §103

Claims 1-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Blondino *et al.* (U.S. Patent No. 6,004,537) in view of Hochrainer *et al.* (U.S. Patent No. 6,150,418). It is alleged that Blondino *et al.* teach a pharmaceutical compsition containing formoterol in combination with budesonide. It is further alleged that Hochrainer *et al.* teaches a pharmaceutical composition containing formoterol suitable for storage in water and ethanol. It is alleged that combination of these references results in the compositions of the instant claims. Applicant respectfully requests reconsideration of this rejection in view of the amendments herein and the following remarks.

Relevant Law

The relevant law is discussed above.

The Instant claims

The instant claims are discussed above.

The teachings of the cited references and differences from the instant claims

Blondino *et al.* teaches combination therapy using formoterol and budesonide in the treatment of asthma. Blondino *et al.* teaches in the Examples MDI formulations (containing a fluoroalkane propellant) of the above-referenced combination. The cited reference does not teach or suggest nebulizable formulations containing formoterol and budesonide. The Office Action points to the title, abstract and claims for the proposition that Blondino *et al.* teaches nebulizable formulations. Applicant respectfully disagrees. The entire teaching of Blondino *et al.* is directed to MDI formulations containing a fluoroalkane propellant. Nowhere does Blondino teach or suggest nebulizable formulations of formoterol and budesonide that have a formoterol concentration of between about 5 μg/mL and about 2 mg/mL, and are stable during long term storage, as required by the instant claims.

Hochrainer *et al.* does not cure this defect in Blondino *et al.* because, while Hochrainer *et al.* teaches highly concentrated compositions of formoterol suitable for storage, it does not teach or suggest compositions having a formoterol concentration of between about 5 μg/mL and about 2 mg/mL that are stable during long term storage. As discussed in detail above, in contrast, Hochrainer *et al.* teaches, at column 2, lines 4-11, that the concentration of formoterol in the compositions taught therein is much higher – at least 10 mg/mL, preferably at least 75, 100 or 250 mg/mL.

Hochrainer *et al.* does not teach or suggest formoterol compositions at lower concentrations, as required by the instant claims, that are stable during long term storage, as required by the instant claims. Therefore, Hochrainer *et al.* does not cure the defects in Blondino *et al.*, and the instant claims are not *prima facie* obvious over the teachings of Blondino *et al.* in view of Hochrainer *et al.* Reconsideration and removal of this ground of rejection is respectfully requested.

REJECTION OF CLAIM 93 UNDER 35 U.S.C. §103

Claim 93 is rejected under 35 U.S.C. §103 as allegedly being unpatentable over Carling *et al.* (U.S. Patent No. 5,674,860) in view of Hochrainer *et al.* (U.S. Patent No. 6,150,418) and further in view of the Physician's Desk Reference entries for albuterol, accolate and Zyflo. It is alleged that combination of these references results in the compositions of the instant claim. Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Instant claim 93

Instant claim 93 is directed to the pharmaceutical composition of claim 1, as described above, further containing one or more of (a) to (j) as follows: (a) a ß2-adrenoreceptor agonist; (b) a dopamine (D2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lypoxygenase inhibitor; or (j) an anti-IgE antibody.

The teachings of the cited references and differences from the instant claim

As discussed in detail above, while Carling *et al.* teaches or suggests nebulizable formulations containing formoterol and budesonide, it does not teach or suggest nebulizable formulations of formoterol and budesonide that have a formoterol concentration of between about 5 μg/mL and about 2 mg/mL, and are stable during long term storage, as required by the instant claim.

Hochrainer *et al.* does not cure this defect in Carling *et al.* because, while Hochrainer *et al.* teaches highly concentrated compositions of formoterol suitable for storage, it does not teach or suggest compositions having a formoterol concentration of between about 5 μg/mL and about 2 mg/mL that are stable during long term storage. In contrast, Hochrainer *et al.* teaches, at column 2, lines 4-11, that the concentration of formoterol in the compositions taught therein is much higher – at least 10 mg/mL, preferably at least 75, 100 or 250 mg/mL.

Hochrainer *et al.* does not teach or suggest formoterol compositions at lower concentrations, as required by the instant claims, that are stable during long term storage, as required by the instant claims. Therefore, Hochrainer *et al.* does not cure the defects in Carling *et al.*, and the instant claims are not *prima facie* obvious over the teachings of Carling *et al.* in view of Hochrainer *et al.* Reconsideration and removal of this ground of rejection is respectfully requested.

Nor do the cited PDR entries cure the defects in Carling *et al.* or Hochrainer *et al.* The cited PDR entries simply state the known use of asthma drugs, but do not teach or suggest how to formulate combinations of these drugs with formoterol and a steroidal anti-inflammatory agent, where the formoterol concentration is between about 5 μg/mL and about 2 mg/mL, and where the composition is stable during long term storage.

Therefore, claim 93 is not *prima facie* obvious over the teachings of Carling *et al.* in view of Hochrainer *et al.* and further in view of the PDR entries for albuterol, accolate and Zyflo. Reconsideration and removal of this ground of rejection is respectfully requested.

REJECTION OF CLAIMS 113-116 AND 120-121 UNDER 35 U.S.C. §103

Claims 113-116 and 120-121 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Carling *et al.* (U.S. Patent No. 5,674,860) in view of Hochrainer *et al.* (U.S. Patent No. 6,150,418) and further in view of the Hardmann *et al.* (Goodman Gilman's *The Pharmacological Basis of Therapeutics*, **1996**, 665) or Leckie *et al.* (*Novel Therapy of COPD*, abstract, Jan. 2000). It is alleged that combination of these references results in the compositions of the instant claim. Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Instant claims 113-116 and 120-121

Instant claim 113 is directed to the pharmaceutical composition of claim 1, as described above, further comprising an anticholinergic agent. Claims 114-116, 120 and 121 are dependent on claim 113 and therefore incorporate all of the limitations of this claim.

The teachings of the cited references and differences from the instant claim

As discussed in detail above, while Carling *et al.* teaches or suggests nebulizable formulations containing formoterol and budesonide, it does not teach or suggest nebulizable formulations of formoterol and budesonide that have a formoterol concentration of between about 5 μg/mL and about 2 mg/mL, and are stable during long term storage, as required by the instant claim.

Hochrainer *et al.* does not cure this defect in Carling *et al.* because, while Hochrainer *et al.* teaches highly concentrated compositions of formoterol suitable for storage, it does not teach or suggest compositions having a formoterol concentration of between about 5 μg/mL and about 2 mg/mL that are stable during long term storage. In contrast, Hochrainer *et al.* teaches, at column 2, lines 4-11, that the concentration of formoterol in the compositions taught therein is much higher – at least 10 mg/mL, preferably at least 75, 100 or 250 mg/mL.

Hochrainer *et al.* does not teach or suggest formoterol compositions at lower concentrations, as required by the instant claims, that are stable during long term storage, as

required by the instant claims. Therefore, Hochrainer *et al.* does not cure the defects in Carling *et al.*, and the instant claims are not *prima facie* obvious over the teachings of Carling *et al.* in view of Hochrainer *et al.* Reconsideration and removal of this ground of rejection is respectfully requested.

Nor do Hardmann *et al.* or Leckie *et al.* cure the defects in Carling *et al.* or Hochrainer *et al.* Hardman *et al.* teaches that ipratropium bromide is an anticholinergic agent useful in treating asthma, but does not teach or suggest how to formulate combinations of this drug with formoterol and a steroidal anti-inflammatory agent, where the formoterol concentration is between about 5 μg/mL and about 2 mg/mL, and where the composition is stable during long term storage. Leckie *et al.* teaches that tiotropium bromide is a known bronchiodilator employed in treating asthma, but does not teach or suggest how to formulate combinations of this drug with formoterol and a steroidal anti-inflammatory agent, where the formoterol concentration is between about 5 μg/mL and about 2 mg/mL, and where the composition is stable during long term storage.

Therefore, instant claims 113-116, 120 and 121 are not *prima facie* obvious over the teachings of Carling *et al.* in view of Hochrainer *et al.* and further in view of Hardmann *et al.* or Leckie *et al.* Reconsideration and removal of this ground of rejection is respectfully requested.

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Applicant respectfully submits that the amendments to the claims herein, the above Remarks, and the enclosed DECLARATION of BANERJEE place this application in condition for allowance. Applicant respectfuly requests that the Examiner contact Applicant's representative should any outstanding issues remain.

Respectfully submitted,

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